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Statin utilisation in a real-world setting: a retrospective analysis in relation to arterial and cardiovascular autonomic function

John D. Sluyter[1], Alun D. Hughes[2], Andrew Lowe[3], Carlos A. Camargo Jr[4] & Robert K. R. Scragg[1]

[1]School of Population Health, University of Auckland, Auckland, New Zealand
[2]Institute of Cardiovascular Sciences, University College London, London, United Kingdom
[3]Institute for Biomedical Technologies, Auckland University of Technology, Auckland, New Zealand
[4]Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, USA

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Correspondence
John Sluyter, School of Population Health, University of Auckland, Private Bag 92019, Auckland, New Zealand. Tel: 64 9 923 6702; Fax: 64 9 373 7503;
E-mail: j.sluyter@auckland.ac.nz

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Abstract

Randomized trials suggest that statin treatment may lower blood pressure and influence cardiovascular autonomic function (CVAF), but the impact of duration of usage, discontinuation, and adherence to this therapy is unknown. We examined these issues with regard to blood pressure (BP)-related variables in a large, population-based study. Participants were 4942 adults (58% male; aged 50–84 years): 2179 on statin treatment and 2763 untreated. Days of utilization, adherence (proportion of days covered ≥0.8), and discontinuation (non-use for ≥30 days immediately prior to BP measurement) of three statins (atorvastatin, pravastatin, and simvastatin) over a period of up to 2 years was monitored retrospectively from electronic databases. Systolic BP (SBP), diastolic BP (DBP), augmentation index, excess pressure, reservoir pressure, and CVAF (pulse rate and BP variability) parameters were calculated from aortic pressure waveforms derived from suprasystolic brachial measurement. Days of statin treatment had inverse relationships with pulse rate variability parameters in cardiac arrhythmic participants (20–25% lower than in statin non-users) and with most arterial function parameters in everyone. For example, compared to untreated participants, those treated for ≥659 days had 3.0 mmHg lower aortic SBP ($P < 0.01$). Discontinuation was associated with higher brachial DBP and aortic DBP (for both, $\beta = 2.0$ mmHg, $P = 0.008$). Compared to non-adherent statin users, adherent users had lower levels of brachial SBP, brachial DBP, aortic DBP, aortic SBP, and peak reservoir pressure ($\beta = -1.4$ to -2.6 mmHg). In conclusion, in a real-world setting, statin-therapy duration, non-discontinuation and adherence associate inversely with BP variables and, in cardiac arrhythmias, CVAF parameters.

Abbreviations

AIx, augmentation index; BMI, body mass index; BP, blood pressure; CVAF, cardiovascular autonomic function; CV, cardiovascular; DBP, diastolic BP; HRV, heart rate variability; PDC, proportion of days covered, PPV, pulse pressure variation; RMSSD, root mean square of successive differences; SBP, systolic BP, SD, standard deviation; ViDA, Vitamin D Assessment.

Introduction

Statins are widely prescribed for their lipid-lowering effects and a recent systematic review found that they may also have small blood pressure (BP)-lowering properties (Briasoulis et al. 2013). In addition, some clinical trials have found that statins may affect measures of cardiovascular autonomic function such as heart rate

variability (HRV) (Millar and Floras 2014). However, the clinical importance of these effects is not clear (Millar and Floras 2014) and merits further investigation. Moreover, the efficacy of statins in real-world settings may be inferior to that seen in trials (Andrade et al. 1995).

Past observational studies have found that adherence to statin therapy correlates negatively with cardiovascular burden, while discontinuation correlates positively (De Vera et al. 2014). This could potentially be attributed, in part, to the effects of statins on BP. But as far as we know, this has not been previously explored. Such an assessment could help understand whether the impact of statin adherence and discontinuation on cardiovascular events is mediated through effects on arterial and cardiovascular autonomic function. Another use of this analysis is that it may provide better recognition of the pharmacology of statins (Reidenberg 2011).

Further, in prior studies evaluating the antihypertensive properties of statins, these effects almost exclusively have been measured by brachial BP. In comparison, few studies have investigated their impact on parameters measured from the aortic pressure waveform such as augmentation index (Manisty et al. 2009; Kanaki et al. 2013; Ballard et al. 2014). This could be important as these variables predict cardiovascular events independently of brachial BP (Vlachopoulos et al. 2010a,b).

The objectives of this study were to examine relationships that patterns of statin use – including discontinuation and adherence – have with brachial BP, measures of arterial function (derived from the aortic pressure waveform), and cardiovascular autonomic function (assessed by HRV and other parameters). This was explored in a population-based study; a real-world setting that may provide different results but complimentary information to that obtained from clinical trials. As the mechanisms for these associations may involve serum cholesterol (Briasoulis et al. 2013; Millar and Floras 2014), we also sought to examine the contributions of this parameter to the relationships, which may give additional insight into this issue.

Materials and Methods

Participants

This study is an analysis of data collected at baseline and retrospectively (before baseline) in the ViDA (Vitamin D Assessment) study, a randomized controlled trial of the effect of vitamin D supplementation on health-related outcomes. Inclusion criteria were men and women aged 50–84 years and resident in Auckland at recruitment. Exclusion criteria included: (1) diagnosis of a terminal illness and/or in hospice care, (2) intending to leave New Zealand during the follow-up period, (3) taking vitamin D supplements (including cod liver oil) of >600 IU per day, (4) history of renal stones, hypercalcemia, or medical conditions that can cause hypercalcemia, and (5) baseline serum calcium >2.50 mmol/L. All baseline data were collected between 2011 and 2012. Ethics approval was provided by the Ministry of Health Multi-region Ethics committee (MEC/09/08/082). Written, informed consent was obtained from each participant. Full details have been published elsewhere (Scragg et al. 2015)

Questionnaire, anthropometric and cholesterol variables

All measurements (both in this section and the next two) were carried out by trained staff using a standardized protocol. Questionnaires administered by interviewers were used to collect data on age, sex, ethnicity (defined by self-identification), smoking, diabetes, and history of cardiovascular disease. Without shoes and in light clothing, height was measured with a stadiometer to the nearest 0.1 cm, and weight with digital scales to the nearest 0.1 kg. Body mass index (BMI) was calculated as body weight (kg)/height $(m)^2$. A blood sample was taken, and collected aliquots were stored at −80°C (−112°F) and later measured for serum total cholesterol on a Siemens Advia 2400 analyser (Siemens Healthcare Diagnostics, Germany).

Arterial function measures

Sitting brachial BP was measured three times after 15 min rest with an Omron T9P oscillometric device (Omron Healthcare, Kyoto, Japan); the mean of the two closest measurements were used for analyses. Participants were considered to be hypertensive if they had a brachial SBP of ≥140 mmHg, a brachial diastolic BP (DBP) of ≥90 mmHg, and/or were receiving antihypertensive medications.

Suprasystolic oscillometry was carried out using a BP+ device (Uscom, Sydney, Australia) (formerly called a R6.5 cardiovascular monitor; Pulsecor, Auckland, New Zealand), with an appropriately sized cuff positioned over the left upper arm. The BP+ device has been shown to: (1) yield central systolic blood pressures that are highly correlated with those assessed by catheter measurement at the ascending aorta or aortic arch (Lin et al. 2012) and, (2) measure central systolic BP with good intratest and intertest reliability (Climie et al. 2012). To improve the quality of the waveforms used in analyses, we decided a priori to exclude readings with a signal-to-noise ratio of <6 dB.

Augmentation index (AIx), an index of arterial stiffness and wave reflection (Davies et al. 2010), was calculated from the aortic pressure waveform using

custom-written Matlab software (Mathworks, Natick, MA). A meta-analysis has shown AIx to be a predictor of CV events (Vlachopoulos et al. 2010a).

Aortic pressure was separated into reservoir and wave components using custom-written Matlab software. Reservoir pressure was calculated from aortic pressure measurements only (Davies et al. 2014), while excess pressure was calculated as measured aortic pressure minus reservoir pressure (Davies et al. 2007). The integrals of the reservoir and excess pressure waveforms (area under these waveforms) over the cardiac cycle was used to calculate reservoir pressure integral and excess pressure integral, respectively. The latter measures pressure associated with excess ventricular work and has been shown to predict CV events independently of brachial SBP (Davies et al. 2014). In addition, peak reservoir and excess pressures were calculated as the maximum values of the reservoir and excess pressure waveforms, respectively (Hametner et al. 2014). The amplitude of the reservoir pressure waveform has been found to associate positively with the risk of cardiovascular events independently of brachial BP (Hametner et al. 2014).

Cardiovascular autonomic function measures

HRV was assessed from the variability of the beat duration of the aortic pressure waveforms derived from the BP+ device. The waveforms spanned approximately 10 seconds; thus analysis was performed on approximately 10–12 pulse intervals, a period adequate for valid measurement of HRV (Thong et al. 2003; Schroeder et al. 2004; Nussinovitch et al. 2011, 2012; Munoz et al. 2015). Two time-domain measures were used: standard deviation (SD) of pulse intervals (in ms; analogous to SD of NN intervals of an electrocardiographic record) and root mean square of successive differences (RMSSD) (Malik et al. 1996; Hilz and Dütsch 2006). RMSSD (in msec) was calculated as the square root of the mean of the squared differences in the duration of successive pulse intervals and reflects parasympathetic activity (Malik et al. 1996; Hilz and Dütsch 2006).

Baroreflex sensitivity was assessed using the sequence method, which establishes the slope of the relationship between changes in pulse interval and SBP across successive cardiac cycles (Parlow et al. 1995; Persson et al. 2001). Pulse intervals were paired with the SBP (systolic pressure wave amplitude) of the preceding cardiac cycle (that is, a one-beat delay), as illustrated elsewhere (Parlow et al. 1995; Persson et al. 2001). Instances in which SBP and pulse intervals (PI) both increased (+PI/+SBP) or decreased (−PI/−SBP) from one beat to the next were detected. Due to the limited number of beats, we did not enforce the practice (Parlow et al. 1995) that these changes had to occur over at least three consecutive beats. The minimum SBP change between pulse intervals that was accepted was 1 mmHg (Kardos et al. 2001). Baroreflex sensitivity (in msec/mmHg) was calculated as the mean of all +PI/+SBP and −PI/−SBP slopes (Kardos et al. 2001).

Aortic pulse pressure variation (PPV) was calculated as (maximum pulse pressure – minimum pulse pressure)/mean pulse pressure from individual beats of the aortic pressure waveform (Lansdorp et al. 2011). Although BP variability is influenced by the mechanical effects of respiration on intrathoracic pressure (Zhang et al. 2002), it may also reflect sympathetic activity (Zhang et al. 2002; Brychta et al. 2007).

Because of the potential influence of cardiac arrhythmias on HRV, analysis of relationships for cardiovascular autonomic function were performed among participants identified as not having a cardiac arrhythmia and results for all others (cardiac arrhythmia identified as being present) were shown separately. While HRV assessment is conventionally applied to people without a cardiac arrhythmia, it can also be carried out to provide informative data in people with one (Van Den Berg et al. 1997). Cardiac arrhythmia was defined as having a history of this condition or if they had a measured RMSSD value of >100 msec, which identifies patients with atrial fibrillation (determined via ECG tracings) with very high sensitivity and specificity (Oh et al. 2013).

Medications

Records of all medicine prescriptions administered for participants before and after their interview dates were collected from the Ministry of Health databases, which includes all dispensed prescriptions. Such data included the medicine name, date dispensed, dose, daily dose, frequency, and days of supply. For the calculations of statin days of supply (which was used to indicate duration of use), discontinuation and adherence, we focused only on prescriptions dispensed prior to (not after) the interview dates (when BP measurements were taken) and with at least 60 days of follow-up.

Discontinuation of statin treatment was defined as continuous non-use of statins in the 30 days immediately prior to BP measurement. Adherence to statin medications was measured by proportion of days covered (PDC), calculated as the total number of days in which they were supplied divided by the observation time interval (Choudhry et al. 2009). The latter was the time difference between statin initiation and the interview date. To account for the utilization of more than one statin, the numerator used to calculate PDC was the number of days in which there was ≥1 statin medication available. Participants with

PDC ≥ 80% were classified as adherent, in accordance with standard practice (Choudhry et al. 2009).

Statistical analysis

Data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC). Because of their positively skewed distributions, excess pressure integral, RMSSD, SD of pulse intervals and baroreflex sensitivity were converted to $\log_e$ for analyses. Differences in the mean values between two groups were compared using analysis of variance and categorical variables were compared using χ^2 tests. Associations between statins and waveform parameters were examined by multiple linear regression. The independent variables for such analyses comprised statin use, antihypertensive treatment, sex, age, ethnicity, smoking, diabetes, history of cardiovascular disease, and BMI. Statin daily dose was not included as an independent variable as it was not significantly related to the outcome variables. Two-sided $P < 0.05$ were considered statistically significant. No *P*-value correction was applied to account for multiple hypothesis tests, as suggested by Rothman (Rothman 1990).

Results

Characteristics of participants stratified by statin treatment are shown in Table 1. Analysis was performed on 4942 adults, 44% of whom received statin therapy. Treated participants received, almost exclusively, atorvastatin and/or simvastatin. Most received simvastatin only ($n = 1206$), fewer took atorvastatin only ($n = 549$) and some received both ($n = 422$). Only four participants were prescribed pravastatin. For all three statins, the mean daily dose over the follow-up period was about 30 mg. The sample comprised individuals who were either currently receiving antihypertensive therapy or were not. Similarly, the hypertensive status of the participants was mixed, with most being hypertensive. Across the two treatment groups, age, sex, ethnicity, hypertension status, antihypertensive treatment, smoking, diabetes, history of cardiovascular disease, and BMI differed. So too did cholesterol, with statin users having lower levels. The time period between statin initiation and follow-up averaged 1.6 years (mean; median was 1.8 years) and was as high as 2.0 years.

Associations with duration of statin use

Table 2 shows relationships of duration of statin use (stratified into approximate quartiles) with measures of arterial and cardiovascular autonomic function. Longer duration of statin treatment (periods of 621 days and above) was associated with lower brachial SBP, brachial DBP, aortic SBP, aortic DBP, and peak reservoir pressure.

Table 1. Characteristics of participants stratified by statin treatment.

Variable	Statin treatment		*P*-value
	Untreated	Treated	
n	2763	2179	
Age (years), mean ± SD	64.9 ± 8.3	68.1 ± 8.0	<0.001
Male (%)	52	65	<0.001
Ethnicity (%)			
European/Other	85	81	<0.001
Maori	5	6	
Pacific	5	8	
South Asian	4	6	
Hypertension (%)	56	82	<0.001
Antihypertensive treatment (%)	23	59	<0.001
Smoking (%)			
Non-smoker	54	49	<0.001
Ex-smoker	40	45	
Current smoker	6	6	
Diabetes mellitus (%)	3	19	<0.001
History of cardiovascular disease (%)	4	25	<0.001
Body mass index (kg/m^2), mean ± SD	27.6 ± 4.9	29.4 ± 5.0	<0.001
Cholesterol, mean ± SD			
Total (mmol/L)	5.3 ± 1.0	4.3 ± 1.0	<0.001
Non-HDL (mmol/L)	3.8 ± 0.9	3.0 ± 0.9	<0.001
Statin treatment (%)			
Atorvastatin		25	
Simvastatin		55	
Atorvastatin + simvastatin		19	
Pravastatin		0.2	
Mean daily dose of statins over follow-up (mg)*			
Atorvastatin		27	
Simvastatin		29	
Pravastatin		32	
Time from statin initiation to follow-up† (days),			
Median ± interquartile range		645 ± 80	
Range		(60–719)	

SD, standard deviation.

*Calculated as cumulative dose dispensed (mg)/cumulative days of supply.

†Follow-up date is baseline interview date, when blood pressure-related variables were measured.

These effect sizes were not large; for example, the differences did not exceed more than 4 mmHg for these parameters. Of the cardiovascular autonomic function parameters, both $\log_e$(RMSSD) and $\log_e$(SD of pulse intervals) were inversely related to duration of statin use (lower with ≥447 days of treatment) among those identified as arrhythmic. The beta-coefficients for these two parameters for ≥447 days of treatment ranged from −0.225 to −0.282, indicating percentage differences of between 20% ($100 \times (1 - e^{-0.225})$) and 25% ($100 \times (1–e^{-0.282})$) for RMSSD and SD of pulse intervals.

Table 2. Arterial and cardiovascular autonomic function in relation to duration of statin use[#].

	Variable	Mean (SE) of untreated (reference)	Mean difference (95% CI) for days of treatment				*P* -value
			≤446 days	447–620 days	621–658 days	≥659 days	
Arterial function measure	*n*	2763	483	557	554	585	
	Brachial SBP (mmHg)	139.0 (0.8)	−0.1 (−2.0, 1.7)	−0.1 (−1.9, 1.6)	−1.2 (−3.0, 0.6)	**−3.5 (−5.3, −1.6)**	**0.005**
	Brachial DBP (mmHg)	77.3 (0.4)	−0.9 (−1.9, 0.1)	−0.6 (−1.6, 0.3)	**−1.3 (−2.3, −0.3)**	**−2.6 (−3.6, −1.6)**	**<0.001**
	Aortic SBP (mmHg)	130.3 (0.8)	0.3 (−1.5, 2.0)	−0.1 (−1.8, 1.7)	−1.0 (−2.8, 0.8)	**−3.0 (−4.8, −1.2)**	**0.01**
	Aortic DBP (mmHg)	78.4 (0.5)	−0.9 (−1.9, 0.1)	−0.7 (−1.7, 0.3)	**−1.3 (−2.3, −0.3)**	**−2.6 (−3.7, −1.6)**	**<0.001**
	Augmentation index	29.9 (0.5)	−0.2 (−1.2, 0.9)	−0.7 (−1.8, 0.4)	−0.4 (−1.5, 0.7)	−0.5 (−1.6, 0.6)	0.70
	Reservoir pressure integral (mmHg.sec)	88.3 (0.8)	0.8 (−0.9, 2.5)	0.2 (−1.5, 0.8)	−0.2 (−1.9, 1.5)	−1.2 (−3.0, 0.5)	0.45
	$\log_e$(EPI (mmHg.sec)) ($\times 10^{-2}$)	105.4 (1.9)	1.9 (−2.3, 6.1)	0.1 (−4.0, 4.2)	1.3 (−2.9, 5.6)	−0.5 (−4.7, 3.8)	0.86
	Peak reservoir pressure (mmHg)	120.6 (0.7)	−0.0 (−1.6, 1.6)	−0.2 (−1.8, 1.4)	−1.2 (−2.9, 0.4)	**−2.8 (−4.4, −1.1)**	**0.02**
	Peak excess pressure (mmHg)	17.5 (0.3)	0.0 (−0.7, 0.7)	0.0 (−0.6, 0.7)	0.2 (−0.5, 0.9)	−0.3 (−1.0, 0.4)	0.80
CV autonomic function measure	No cardiac arrhythmia						
	n	2146	361	399	382	381	
	$\log_e$(RMSSD (msec)) ($\times 10^{-2}$)	332.8 (3.5)	−0.6 (−7.9, 6.7)	1.0 (−6.3, 8.3)	5.1 (−2.6, 12.8)	1.7 (−6.2, 9.6)	0.76
	$\log_e$(SD of pulse intervals (msec)) ($\times 10^{-2}$)	236.2 (3.8)	1.3 (−6.7, 9.4)	1.6 (−6.4, 9.6)	11.9 (3.5, 20.3)	4.6 (−4.1, 13.3)	0.09
	$\log_e$(BRS (msec/mmHg)) ($\times 10^{-2}$)	130.4 (4.7)	12.2 (2.3, 22.1)	3.7 (−6.3, 13.6)	−0.7 (−11.2, 9.8)	−3.5 (−14.3, 7.3)	0.10
	Aortic pulse pressure variation ($\times 10^{-2}$)	36.3 (0.8)	−0.9 (−2.6, 0.8)	−0.6 (−2.3, 1.1)	**−2.0 (−3.8, −0.2)**	0.1 (−1.8, 1.9)	0.21
	Cardiac arrhythmia present						
	n	617	122	158	172	204	
	$\log_e$(RMSSD (msec)) ($\times 10^{-2}$)	509.8 (10.5)	−16.1 (−40.1, 8.0)	**−25.5 (−47.9, −3.0)**	**−22.6 (−44.4, −0.7)**	**−28.2 (−49.3, −7.1)**	**0.04**
	$\log_e$(SD of pulse intervals (msec)) ($\times 10^{-2}$)	395.5 (9.8)	−16.4 (−38.9, 6.1)	**−24.1 (−45.1, −3.2)**	**−22.5 (−43.0, −2.1)**	**−25.4 (−45.2, −5.7)**	**0.04**
	$\log_e$(BRS (msec/mmHg)) ($\times 10^{-2}$)	185.6 (10.0)	−9.6 (−32.5, 13.3)	−2.3 (−23.7, 19.1)	−12.6 (−33.6, 8.3)	−14.7 (−34.6, 5.2)	0.56
	Aortic pulse pressure variation ($\times 10^{-2}$)	45.2 (1.8)	−0.2 (−4.3, 3.8)	−1.4 (−5.2, 2.4)	**−4.4 (−8.1, −0.7)**	−2.3 (−5.8, 1.3)	0.20

SE, standard error; CI, confidence intervals; EPI, excess pressure integral; CV, cardiovascular; RMSSD, root mean square of successive differences; SD, standard deviation; BRS, baroreflex sensitivity.
[#]Adjusted for age, sex, ethnicity, antihypertensive medication use, smoking, diabetes, history of cardiovascular disease and BMI. *P*-values test for differences across the 5 groups; 95% confidence intervals that do not encompass zero and significant main effects ($P < 0.05$) are in bold.

Influence of discontinuation

Discontinuation was then added to the models for the abovementioned results on statin duration (illustrated in Table 2) in order to evaluate the impact of this on the BP-related variables. In addition, this analysis was restricted to treated participants only to enable direct comparisons between discontinuers and non-discontinuers who received statin therapy. Altogether, the covariates for these analyses were days of supply, as well as demographics, antihypertensive use, smoking, diabetes, history of cardiovascular disease, and BMI. These results are provided in Table 3. This table shows that, for the same duration of use, statin discontinuation ≥30 days immediately prior to BP measurement was unrelated to most arterial function parameters and all cardiovascular autonomic function variables. But it was associated with slightly higher levels (by 2 mmHg) of brachial DBP and aortic DBP.

Relationships with adherence

To investigate the impact of adherence to statin medication on waveform parameters, models for Table 3 were reanalyzed with PDC groups (indicative of adherence) as independent variables instead of discontinuation and days of supply (Table 4). Among participants who received statin prophylaxis, people who were adherent to such treatment (PDC ≥ 0.8) had slightly lower BP and peak reservoir pressure than those who were non-adherent (PDC < 0.8). For brachial DBP and aortic DBP, this was particularly the case among people who were most adherent (PDC = 1). Out of the cardiovascular autonomic function variables, aortic PPV was lower in the adherent group among arrhythmic participants but all other measures were unrelated to adherence.

Impact of cholesterol

As expected, total cholesterol had inverse, dose-dependent relationships with duration of statin use (Table S1). The analyses for Table 2 were repeated, adjusting for total cholesterol (Table S1). Comparison of both tables shows that statistical adjustment for cholesterol notably attenuated relationships of arterial function parameters and eliminated all of these except for DBP variables (Table S1). In contrast, relationships of cardiovascular

Table 3. Arterial and cardiovascular autonomic function in relation to statin discontinuation, adjusted for days of supply[#].

	Variable	Mean (SE) of non-discontinuers (reference)	Mean difference (95% CI) for discontinuers	*P*-value
Arterial function measure	*n*	1901	278	
	Brachial SBP (mmHg)	138.7 (0.9)	1.3 (−1.3, 4.0)	0.33
	Brachial DBP (mmHg)	75.1 (0.5)	**2.0 (0.5, 3.5)**	**0.008**
	Aortic SBP (mmHg)	130.3 (0.9)	1.5 (−1.1, 4.1)	0.27
	Aortic DBP (mmHg)	76.2 (0.5)	**2.0 (0.5, 3.5)**	**0.008**
	Augmentation index	29.1 (0.5)	0.2 (−1.3, 1.8)	0.76
	Reservoir pressure integral (mmHg.sec)	88.0 (0.9)	0.7 (−1.8, 3.3)	0.57
	$\log_e$(EPI (mmHg. sec)) ($\times 10^{-2}$)	110.3 (2.2)	−4.0 (−10.4, 2.4)	0.22
	Peak reservoir pressure (mmHg)	120.2 (0.8)	2.0 (−0.4, 4.4)	0.10
	Peak excess pressure (mmHg)	18.0 (0.4)	−0.6 (−1.7, 0.5)	0.26
CV autonomic function measure	No cardiac arrhythmia			
	n	1325	198	
	$\log_e$(RMSSD (msec)) ($\times 10^{-2}$)	340.9 (4.1)	−3.5 (−15.0, 8.0)	0.55
	$\log_e$(SD of pulse intervals (msec)) ($\times 10^{-2}$)	247.3 (4.6)	−6.4 (−19.6, 6.7)	0.34
	$\log_e$(BRS (msec/mmHg)) ($\times 10^{-2}$)	131.6 (5.3)	−0.3 (−15.3, 14.7)	0.97
	Aortic pulse pressure variation ($\times 10^{-2}$)	35.4 (0.9)	1.2 (−1.5, 3.8)	0.38
	Cardiac arrhythmia present			
	n	576	80	
	$\log_e$(RMSSD (msec)) ($\times 10^{-2}$)	485.9 (11.8)	7.2 (−27.2, 41.5)	0.68
	$\log_e$(SD of pulse intervals (msec)) ($\times 10^{-2}$)	372.9 (11.1)	6.1 (−26.3, 38.6)	0.71
	$\log_e$(BRS (msec/mmHg)) ($\times 10^{-2}$)	161.3 (11.1)	13.5 (−18.7, 45.7)	0.41
	Aortic pulse pressure variation ($\times 10^{-2}$)	42.3 (1.9)	3.1 (−2.4, 8.7)	0.27

SE, standard error; CI, confidence intervals; EPI, excess pressure integral; CV, cardiovascular; RMSSD, root mean square of successive differences; SD, standard deviation.

[#]Adjusted for duration of use, age, sex, ethnicity, antihypertensive medication use, smoking, diabetes, history of cardiovascular disease and BMI. *P*-values test for differences across the 2 groups. 95% confidence intervals that do not encompass zero and significant main effects ($P < 0.05$) are in bold.

Table 4. Arterial and cardiovascular autonomic function in relation to statin adherence[#].

	Variable	Mean (SE) of non-adherent (reference) PDC < 0.8	Mean difference (95% CI) for adherent PDC = 0.8–0.99	PDC = 1	*P*-value
Arterial function measures	*n*	389	605	1185	
	Brachial SBP (mmHg)	140.5 (1.2)	**−2.6 (−5.0, −0.2)**	−1.8 (−4.0, 0.4)	0.09
	Brachial DBP (mmHg)	76.6 (0.7)	**−1.4 (−2.7, −0.1)**	**−1.9 (−3.1, −0.7)**	**0.009**
	Aortic SBP (mmHg)	132.2 (1.2)	**−2.6 (−4.9, −0.3)**	−2.0 (−4.2, 0.2)	0.08
	Aortic DBP (mmHg)	77.7 (0.7)	**−1.4 (−2.7, −0.1)**	**−1.9 (−3.1, −0.6)**	**0.01**
	Augmentation index	29.4 (0.7)	−0.6 (−2.0, 0.8)	−0.2 (−1.5, 1.2)	0.59
	Reservoir pressure integral (mmHg.sec)	88.7 (1.2)	−1.0 (−3.2, 1.3)	−0.7 (−2.9, 1.4)	0.69
	$\log_e$(EPI (mmHg.s)) ($\times 10^{-2}$)	108.6 (2.9)	−1.3 (−6.9, 4.3)	3.5 (−1.8, 8.8)	0.08
	Peak reservoir pressure (mmHg)	122.3 (1.1)	**−2.6 (−4.7, −0.5)**	**−2.3 (−4.3, −0.3)**	**0.04**
	Peak excess pressure (mmHg)	17.7 (0.5)	−0.0 (−1.0, 0.9)	0.6 (−0.3, 1.5)	0.18
CV autonomic function measures	No cardiac arrhythmia				
	n	277	436	810	
	$\log_e$(RMSSD (msec)) ($\times 10^{-2}$)	337.7 (5.3)	0.9 (−9.2, 11.1)	5.7 (−3.9, 15.3)	0.36
	$\log_e$(SD of pulse intervals (msec)) ($\times 10^{-2}$)	243.9 (6.0)	0.7 (−10.9, 12.3)	5.6 (−5.4, 16.5)	0.46
	$\log_e$(BRS (msec/mmHg)) ($\times 10^{-2}$)	135.3 (6.9)	1.8 (−11.4, 15.0)	−8.6 (−21.1, 3.8)	0.11
	Aortic pulse pressure variation ($\times 10^{-2}$)	36.5 (1.2)	−1.4 (−3.7, 0.9)	−1.4 (−3.6, 0.8)	0.40
	Cardiac arrhythmia present				
	n	112	169	375	
	$\log_e$(RMSSD (msec)) ($\times 10^{-2}$)	502.4 (15.7)	−20.3 (−50.3, 9.7)	−21.4 (−49.5, 6.7)	0.30
	$\log_e$(SD of pulse intervals (msec)) ($\times 10^{-2}$)	387.4 (14.7)	−15.8 (−44.0, 12.5)	−20.1 (−46.6, 6.5)	0.33
	$\log_e$(BRS (msec/mmHg)) ($\times 10^{-2}$)	176.6 (14.9)	−11.5 (−40.1, 17.0)	−21.5 (−48.2, 5.3)	0.27
	Aortic pulse pressure variation ($\times 10^{-2}$)	47.3 (2.5)	**−6.1 (−10.9, −1.3)**	**−5.8 (−10.4, −1.3)**	**0.02**

SE, standard error; CI, confidence intervals; EPI, excess pressure integral; PDC, proportion of days covered; CV, cardiovascular; RMSSD, root mean square of successive differences; SD, standard deviation.

[#]Adjusted for age, sex, ethnicity, antihypertensive medication use, smoking, diabetes, history of cardiovascular disease, and BMI. *P* -values test for differences across the three groups.

95% confidence intervals that do not encompass zero and significant main effects ($P < 0.05$) are in bold.

autonomic functions in arrhythmic participants were not reduced by adjustment for cholesterol.

Associations in hypertensive participants

The analyses for Table 2 were repeated for hypertensive participants only and these results are displayed in Table S2. The beta-coefficients for the hypertensive sample (Table S2) were larger than for the corresponding analyses in the total sample (Table 2). Fewer than 621 days of treatment was inversely related to arterial function measures (SBP, DBP, and peak reservoir pressure variables) in the hypertensive sample (Table S2), unlike in the total sample (Table 2).

Discussion

In a large, population-based study, we found that long periods of statin utilization were associated with lower levels of most arterial function parameters (SBP, DBP, and peak reservoir pressure variables). Admittedly, the sizes of these effects were not substantial. For example, the largest difference observed with aortic DBP was 2.6 mmHg, which represents 3% of the average value among untreated participants (Table 2). For the same duration of use, DBP variables were higher among those who discontinued use for at least 30 days immediately prior to BP measurement. Statin use was associated with lower levels of some arterial function parameters in people who were adherent to such therapy. Finally, duration of use was inversely related to HRV parameters in people with diagnosed or suspected cardiac arrhythmias. Specifically, RMSSD and SD of pulse intervals were 20–25% lower in statin users with ≥447 days of treatment, indicating that these differences were of large magnitude.

The modest, inverse relationships between statins and brachial BP concur with findings of clinical trials (Mangat et al. 2007). For example, a meta-analysis found that the effect size with statin use was −2.62 mmHg (95% confidence interval: −3.41 to −1.84 mmHg) for SBP and −0.94 mmHg (95% confidence interval: −1.31 to −0.57 mmHg) for DBP (Briasoulis et al. 2013), which is line with our results (Table 2). Thus, we extend the trial findings by showing this to be the case in a real-world

setting. Clinical trials have reported negative associations with AIx (Manisty et al. 2009; Kanaki et al. 2013), but our relationships for this parameter were not statistically significant, although they were in the same direction. Our work further adds to the literature by demonstrating, for the first time, that statin use is associated with lower reservoir pressure parameters (peak and area) but not excess pressure measures (Table 2). The absence of an effect on the latter suggests that excess pressure variables may be difficult to modify with statins, but clinical trials are required to confirm this.

This study provides new insight into the impact of discontinuation of statin therapy on BP, which has not been previously explored. The finding that some BP variables were higher among those who discontinued use for ≥30 days immediately prior to BP measurement, even after adjustment for days of supply, suggests that cessation of therapy may confer a small increase in BP-related cardiovascular risk. In support of this, studies have reported that statin discontinuation is associated with an elevated risk of cardiovascular events (De Vera et al. 2014). In fact, a few studies have reported that this effect occurs when the treatment stoppage interval is as short as 1 month (De Vera et al. 2011, 2012), which is the lower limit for the time-period (30 days prior to BP measurement) that we used to define discontinuation. Further, if statins had long-term influences on BP (a low "off-rate"), one might expect discontinuation to have no impact (Lowy et al. 2011). But since it was associated with higher levels of some waveform parameters, this could mean that effects are more short-term (<1 month). The relevance and importance of our findings are increased because clinical trials of discontinuation are unlikely to be carried out for ethical reasons and the prevalence of discontinuation is high (reported to be ≥50% in most studies) (De Vera et al. 2014).

Adherence to statin therapy is important as this influences cardiovascular morbidity (De Vera et al. 2014), but it is not known whether this relationship is mediated through influences on BP. We show that this could contribute since our results demonstrate that adherent use was associated with lower levels of SBP, DBP, and peak reservoir pressure variables. However, as these BP-related differences were not large (Table 4), the predicted risk attributable to these is unlikely to account for all the adverse consequences of poor adherence to statins.

Prior work investigating the influence of statins on cardiovascular autonomic function comprised small (predominantly $n < 50$) clinical trials of predominantly short duration (mostly ≤8 weeks) and their findings have been inconsistent (Millar and Floras 2014). Our large and real-life study of a few years of statin prescription data therefore helps to provide additional insight into their efficacy in clinical practice. To interpret our findings for cardiovascular autonomic function parameters, we note that HRV is raised in our arrhythmic participants (Tables 2–4) and elevated HRV is associated with an increased risk of both atrial fibrillation (Wiesel et al. 2004; Oh et al. 2013) and cardiac mortality (De Bruyne et al. 1999). Thus, in people with arrhythmias, a significantly lower HRV – which we observed with statin use (up to a 25% difference) – could reduce risk of adverse cardiovascular outcomes. In support of this, statins have antiarrhythmic effects and decrease the risk of atrial fibrillation (Fauchier et al. 2008), and some antiarrhythmic drugs lower HRV (Malik et al. 1996). This could occur through modulation of the autonomic nervous system, as well as through reductions in inflammation and oxidative stress (Fauchier et al. 2008). Clinical trials that examine whether statins reduce HRV in patients with cardiac arrhythmias are required to verify our findings and evaluate their prognostic significance.

The contributions of serum cholesterol to the effects of statins on arterial and cardiovascular autonomic function parameters are unclear (Briasoulis et al. 2013; Millar and Floras 2014) and investigation into this has been recommended (Millar and Floras 2014). We add understanding to this issue by showing that cholesterol made large contributions to arterial function associations and, independently of it, statin duration of use was related (inversely) to DBP variables. In contrast, the inverse HRV relationships in arrhythmic participants were minimally influenced by cholesterol and independent of it. Consistent with this, randomized controlled trial data suggest that statins reduce sympathetic activity independently of cholesterol (Lewandowski et al. 2014). This implies that relying on cholesterol to capture the beneficial impact of statin therapy may capture influences on arterial function measures well but underestimate the effects on HRV parameters.

As lipophilic statins reduce efferent sympathetic outflow (Millar and Floras 2014), their hypotensive effects may be greater in people with hypertension. This pattern is evident in our data when comparing results for the total sample (Table 2) with those for hypertensives (Table S2). Therefore, studies that investigate the antihypertensive effects of statins in normotensive people may underestimate benefits that occur in hypertensives.

Some limitations and strengths of this study deserve mention. First, although we adjusted for a wide range of covariates in our analyses, causal inferences in the findings cannot be made as it is possible that statin utilization is related to other unknown factors that also affect arterial function. Nevertheless, as discussed above, the results of this study are consistent with those from clinical trials. For example, brachial BP was, at most, nearly 4 mmHg

lower with statin therapy than without it (Table 2), which concurs with effect sizes reported in clinical trials (Briasoulis et al. 2013). Furthermore, the observation that cholesterol levels varied with statin use in a manner that would be expected (Tables 1 and S1–S2) indicates that this effect, at least, is not obscured by unobserved confounders. Second, our cardiovascular autonomic function measures were collected from BP recordings over a period of typically 10–12 sec and, while several studies show that time-domain measures (particularly RMSSD) calculated from 10-sec recordings can be used to reliably estimate HRV, a longer sampling interval (typically 5-min) is preferable (Thong et al. 2003; Schroeder et al. 2004; Nussinovitch et al. 2011, 2012; Munoz et al. 2015). Third, the pulse rate variability parameters in our study were limited to time-domain measures and did not include frequency-domain variables, which may capture different aspects of autonomic function (Hilz and Dütsch 2006). Fourth, in baroreflex sensitivity measurement with the sequence technique, the minimum number of consecutive cardiac cycles for a baroreflex sequence (pairs of unidirectional changes in pulse interval and SBP) is traditionally three (Parlow et al. 1995), but we set the lower limit to one in our calculations. While our modified approach is not ideal, its validity is supported by the finding that, in statistical models of ours, baroreflex sensitivity was inversely related to age, BMI and smoking, brachial SBP, and brachial DBP (data not shown); consistent with research that used the conventional sequence method approach (minimum of three beats for a sequence) for baroreflex sensitivity measurement (Kardos et al. 2001). Finally, the strengths of this study include the large, population-based sample, the variety of waveform parameters as endpoints, and the comparatively long follow-up periods (nearly 2 years of statin prescription data) for many people.

In summary, in a real-world setting and independently of cholesterol, duration of statin use had sizeable, inverse relationships with HRV parameters in those with diagnosed or suspected cardiac arrhythmias. Among everyone, adherence and longer periods of utilization were associated with lower, more favorable levels of most arterial function parameters: brachial and aortic SBP and DBP, and peak reservoir pressure. Conversely, discontinuation for at least 1 month immediately prior to baseline was related to higher levels of brachial and aortic DBP. These arterial function associations were almost exclusively cholesterol-dependent, although still independent of cholesterol in some cases.

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Disclosure

Andrew Lowe is a shareholder in and has consulted for Uscom Limited.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Arterial and cardiovascular autonomic function in relation to duration of statin use, adjusted for total cholesterol.

Table S2. Arterial and cardiovascular autonomic function in relation to duration of statin use – among hypertensive participants.